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EXAMINER	
LAMBERTSON, DAVID A	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 10/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/029,471	KHODADOUST, MEHRAN M.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53-61,63-68 and 79-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53-61,63-68 and 79-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 29, 2005 has been entered.

Receipt is acknowledged of a reply to the previous Office Action, filed July 29, 2005. Amendments were made to the claims. Specifically, claims 1-52 and 69-78 were cancelled.

Claims 53-61, 63-68 and 79-82 are pending and under consideration in the instant application. Any rejection of record in the previous Office Action, mailed December 23, 2004, that is not addressed in this action has been withdrawn.

Although a number of the rejections set forth below are maintained, they are set forth as new rejections to further clarify the nature of the rejections, and to address limitations that were not previously addressed. Insofar as Applicant's arguments are considered pertinent to the following rejections, those arguments (particularly with regard to the use of the Baetscher reference) will be addressed.

Information Disclosure Statement

The information disclosure statement filed July 29 2005 has been considered, and a signed and initialed copy of the form PTO-1449 is attached to this Office Action.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following rejections are based on the following interpretation of the term "reporter." Absent an explicit definition to the contrary, a "reporter" is any polypeptide sequence (as encoded by a polynucleotide sequence) that can be detected by conventional means. This includes colorimetric assays, bio- or chemiluminescence assays, as well as screening assays such as selection on a particular growth medium (such as a positive or negative selection marker). Because any polypeptide sequence can be detected by some means (e.g., by measuring its enzymatic activity, or detecting it with specific antibodies), any polypeptide meets the limitation of being a "reporter."

Claims 53, 56, 57, 59, 60, 63-68 and 79-82 are rejected under 35 U.S.C. 102(b) as being anticipated by Baetscher (as cited previously). It is noted that this rejection is maintained for the reasons set forth in the previous Office Action, except for the fact that claims 57, 60 and 68 are added in view of the interpretation of the claim set forth below.

As it regards claims 53, 56, 59, 63-67 and 79-82, the rejections are maintained as previously set forth in the rejection mailed December 23, 2004. To reiterate:

Baetscher teaches a gene trap nucleic acid construct comprising the following elements in a 5'-to-3' orientation:

Splice acceptor---IRES---Neo-HSV-TK (see for example Figure 2).

Because the Neomycin resistance gene is a positive selection marker (as set forth in dependent claim 80) and HSV-TK is a negative selection marker (as set forth in dependent claim 79), the above specific construct teaches the following general formula:

Splice acceptor---IRES---positive selection---negative selection.

This nucleic acid construct is then placed within the context of a retroviral vector construct (see for example column 12, lines 34-55), which along with LTR elements (i.e., integration sequences) additionally contains selectable or assayable markers, including those useful in "fluorescence activated cell sorting" (see for example column 8, lines 50-57). Thus, the general formula of the nucleic acid construct taught by Baetscher has the overall general formula of:

Splice acceptor---IRES---positive selection---negative selection---reporter. This general construct anticipates claim 53.

Specifically, in order to get proper translation of the positive/negative selection marker, a translation stop codon must be present at the end of the coding sequence. Indeed, Baetscher also anticipates adding a Stop codon downstream from the selectable markers (see for example column 5, lines 22-29). Furthermore, in order to get expression of the reporter, a promoter element must be operatively linked to the reporter gene. Thus, the construct taught by Baetscher can further be visualized as having the following general formula:

Splice acceptor---IRES---positive selection---negative selection---STOP---Promoter---reporter. This construct anticipates claim 56.

Importantly, as set forth above, the retroviral vector further comprises selectable or assayable markers, including those useful in "fluorescence activated cell sorting" (see for example column 8, lines 50-57). Such a reporter can be a "protein that spontaneously emits light...Green Fluorescent Protein (GFP)" (see for example column 10, lines 12-19), which anticipates both claims 81 and 82.

Notably, the Neo-HSV-Tk marker is not operably linked to a promoter within the context of the nucleotide construct; i.e., it is a promoterless marker construct (see for example column 5, lines 44-67). As a result, the selection markers are only expressed when the construct integrates into the genome of a host cell, and the selection markers become operably linked to an endogenous promoter element of the host cell (see for example column 13, lines 25-33). Thus, Baetscher also teaches a host cell comprising the claimed nucleic acid constructs/vectors.

Finally, Baetscher teaches a particular vector having the following formula:

Splice acceptor---IRES---Neo-HSV-TK---STOP---Promoter---Ampicillin. This vector anticipates claim 59.

Support for such a vector comes both from the above analysis of the teachings, and from column 12, lines 63-67, which indicate that the retroviral vector of the element can contain "regulatory elements suitable for propagation and selection in *E. coli*." This includes the Ampicillin resistance gene, which can serve as a positive selection marker (in the presence of ampicillin), and a prokaryotic promoter (i.e., regulatory element) to allow the expression of the Ampicillin resistance gene. Furthermore, given the interpretation of a reporter molecule set forth above, the Neomycin resistance gene can also be a reporter, allowing for the following formula:

Splice acceptor---IRES---reporter---negative marker---STOP---Promoter---positive marker,

which is a particular embodiment of claim 59.

In conclusion, Baetscher meets all of the limitations of the above indicated claims as amended, and therefore anticipates the claimed invention.

As it regards newly included claims 57, 60 and 68, it is noted that the claim reads on nucleic acids that have no specific size boundaries, given the use of "comprising" language. When the constructs described by Baetscher are transformed into a host cell, the constructs integrate randomly into the chromosomes of said host cell (see for example column 9, lines 19-33 and column 13, lines 25-33). In certain instances, the chromosome into which the nucleic acid integrates will also contain a nucleic acid encoding a transcription factor, as chromosomes naturally encode the endogenous transcription factors of a host cell. Thus, Baetscher teaches a host cell comprising a first nucleic acid having a positive selection marker and a negative selection marker (both present in the integration construct), and a segment encoding a transactivator polypeptide (e.g., transcription factor) that is endogenous to the sequence into which the construct integrates; this is by virtue of teaching the integration of their constructs into a chromosome (which is itself a nucleic acid). By definition, this meets the limitation of a nucleic acid comprising a positive selection marker, a negative selection marker and a transactivator polypeptide (as in claims 57 and 60), and the corresponding host cell (as in claim 68). Furthermore, because said transactivator polypeptide is endogenous to the cell, there will necessarily be present a second nucleic acid that binds the transcription factor, wherein that nucleic acid segment serves as a promoter element that is directly responsive to the transactivator polypeptide. Thus, Baetscher also anticipates claims 60 and 68, previously not indicated as rejected by this reference, thus necessitating the new rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 53, 56, 57, 59, 60, 63-68, 79-82 and 54*, 55* are also rejected under 35 U.S.C. 103(a) as being unpatentable over Baetscher (as recited in the rejection of claims 53, 56, 57, 59, 60, 63-68 and 79-82 under 35 USC § 102(b)) in view of MPEP § 2144.04 (VI)(C). Note- "*" represents those claims that are specifically represented by the combination of references; claims lacking an asterisk are also rejected by the combination of references by virtue of their being rejected by the single reference.

Baetscher teaches all of the elements set forth above in the rejection under 35 USC § 102(b); this includes all of the specific elements set forth as limitations in each embodiment of the instant claims. However, Baetscher does not specifically teach the different orientations as set forth in each embodiment of the claims. For example, claim 54 is directed distinctly to the first embodiment of claim 53; although Baetscher teaches the presence of each element set forth in the first embodiment of claim 53, it does not set forth the specific order. It is simply that a different order of the elements is used. The same statement is true of claim 55

MPEP § 2144.04 (VI)(C) cites that the rearrangement of parts is an obvious matter of design choice, unless the variation modifies the operation of the device. In the instant case, the particular elements set forth in the claimed nucleic acids are not indicated as altering the function of the claimed nucleic acids based upon their positioning. Indeed, the specification teaches that

each nucleic acid is to be used for the same function, the generation of a library of cells under the control of specific regulatory elements (see pages 5-6 of the instant specification). Because each of the nucleic acids set forth in the claims have the same elements and the same function, it would be obvious for the ordinary skilled artisan to alter the sequence of the elements within the nucleic acids as a matter of design choice. This is merely an aesthetic choice, and confers no patentable functional distinction on the vectors (based on the instant disclosure). The ordinary skilled artisan would have been motivated to alter the sequence of the elements within the nucleic acids because the function of each element is the same as in the particular orientation taught by Baetscher, and such rearrangements have been determined to be patentably equivalent. Absent evidence to the contrary (i.e., some teaching in the instant specification indicating that each particular order of elements confers a patentably distinct function on the claimed nucleic acids), the ordinary skilled artisan would have had a reasonable expectation of success when altering the order of the elements taught by Baetscher to arrive at each of the claimed embodiments of the invention.

Claims 53, 56, 57, 59, 60, 63-68, 79-82 and 56*, 58* and 61* are rejected under 35 U.S.C. 103(a) as being unpatentable over Baetscher (as recited in the rejection of claims 53, 56, 57, 59, 60, 63-68 and 79-82 under 35 USC § 102(b)) in view of Zambrowicz *et al.* (US 6,436,707; see entire document; henceforth Zambrowicz)). Note- "*" represents those claims that are specifically represented by the combination of references; claims lacking an asterisk are also rejected by the combination of references by virtue of their being rejected by the single reference.

Baetscher teaches all of the elements set forth above in the rejection of claims 53, 56, 57, 59, 60, 63-68 and 79-82 under 35 USC § 102(b). Briefly, Baetscher teaches the construction of gene trap vectors comprising a splice acceptor site, positive/negative selection markers, IRES elements, Stop codons, polyadenylation sequences and reporter genes, in various orders. However, Baetscher does not teach the specific use of (a) a yeast promoter 5' to a positive selectable marker (as in claim 56) or (b) the use of recombinase sequences in their nucleic acids (as in claims 58 and 61).

Zambrowicz teaches the construction of gene trap vectors (see for example the Abstract, column 2, lines 10-31), comprising many of the elements set forth in the teachings of Baetscher such as splice acceptor sites, IRES elements and positive/negative selectable marker genes. The gene trap vectors are to be used in a variety of host cells including yeast (see for example column 4, lines 30-33 and 56-63). The gene trap vectors are also designed to contain a marker gene to facilitate the tracking and identification of transformed cells (see for example column 6, lines 20-38)); in the instance where yeast cells are used, it would be obvious to use a yeast promoter operably linked 5' to the positive selection marker (such as in claim 56 of the instant invention) in order to ensure expression of the marker in the host cell of interest (lest the marker gene be non-functional in its intended use). Zambrowicz also teaches the use of recombinase sites within the gene trap cassette (see for example column 8, lines 40-55), and indicates that these sites have the advantage of allowing the conditional activation or deactivation of the gene trap (see for example column 10, lines 22-30).

It would have been obvious for the ordinary skilled artisan to combine the teachings of Baetscher and Zambrowicz to arrive at the instantly claimed nucleic acids because the teachings

both concern the making and using of gene trap vectors, and thus are clearly combinable. The ordinary skilled artisan would have been motivated to combine the teachings to use a vector having a yeast promoter in order to perform the gene trap method of Baetscher in yeast, a model genetic organism. The ordinary skilled artisan would have been further motivated to combine the teachings of Baetscher and Zambrowicz to utilize recombinase sites because Zambrowicz clearly teaches the advantage of being able to turn on and off the gene trap mechanism using said sites. Absent evidence to the contrary, the ordinary skilled artisan would have had a reasonable expectation of success when combining the teachings of Baetscher and Zambrowicz.

Response to Arguments

Applicant's arguments filed July 29, 2005 have been fully considered but they are not persuasive. Applicant provides the following grounds of traversal regarding the rejections in view of Baetscher:

1. Applicant asserts that Baetscher actually teaches that the selectable markers are interchangeable with the positive and negative selection markers based on a disclosure at column 10, lines 12-13; therefore Baetscher does not describe the vectors that further comprise a selectable marker (see Applicant's arguments on page 11 of the response).

2. Applicant argues that Baetscher fails to teach that "the negative and positive selection markers are immediately 3' to the splice acceptor site," which allows for efficient expression of the marker genes (see for example page 12 and 16 of Applicant's arguments).

3. Applicant argues that the correct orientation of the nucleic acids set forth in the claims is not taught by Baetscher (see for example pages 12-13 of Applicant's arguments).

4. Applicant argues that the dependent claims cannot be rejected based upon previous arguments that the independent claims cannot be rejected (see for example pages 16 and 20 of Applicant's arguments).

Applicant's arguments have been considered but are not found convincing for the following reasons:

1. First, it is noted that column 10, lines 12-13 does not indicate that selectable markers and negative/positive markers are interchangeable, but merely that they can be detected. There is no statement in the teachings of Baetscher indicating that selectable markers are merely substitutes for positive/negative selection markers. Thus, stating that the markers are meant to be interchangeable based solely on a statement indicating that each can be detected is pure conjecture.

Indeed, in the previous rejection it was set forth that Baetscher teaches vectors containing regulatory elements suitable for propagation and selection in *E. coli*, including the Ampicillin resistance gene operably linked to a prokaryotic promoter (see for example page 5 of the previous Office Action). This necessarily represents a selectable marker within the nucleic acids taught by Baetscher that is distinct from the positive and negative selection markers used in the gene trap cassette, as there is absolutely no indication in Baetscher that this selectable marker is interchangeable with the positive and negative selection markers. As such, the argument is not found to be convincing.

2. The language "immediately 3' to the splice acceptor site" does not appear in any of the rejected claims. It is not persuasive to argue that a reference does not teach a limitation that itself is not present in the claims. Furthermore, the claims merely teach that the positive and

negative selection marker are *somewhere* 3' to the splice acceptor site; this could be a few bases, hundreds of bases, or even millions of bases. Baetscher clearly teaches that the positive and negative selection markers are 3' to the splice acceptor site (as evidenced by Applicant's indication that they do on page 12- Applicant clearly interprets the vector taught by Baetscher as being (in the very least) SA—IRES--POSITIVE SELECTION--NEGATIVE SELECTION), and thus anticipate the claims.

3. As it regards the specific orientation of the elements as set forth in the vectors, it is first noted that Baetscher indeed has the formula as set forth in claim 53, embodiments 2 and 3, when considering the presence of the selectable marker in the vectors (such as Ampicillin; see item #1) taught by Baetscher.

Additionally, the Office has presented the disclosure of MPEP § 2144.04 (VI)(C), which indicates that rearrangements of elements are obvious, unless some unknown function is specifically served by a particular orientation. Thus, as it regards embodiments 1 and 4 of claim 53 (as well as some dependent claims), the orientation of the elements is simply an obvious aesthetic variation. As such, this argument is not found persuasive.

4. Finally, it is noted that Applicant's arguments regarding the impropriety of the rejection of the independent claims have not found to be persuasive. As a result, it is not persuasive to argue that the non-rejectability of independent claims is sufficient to traverse the rejection of dependent claims.

Allowable Subject Matter

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (571) 272-0771. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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